PATENT
Attorney Docket No.: 020801-000720US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Examiner: Woitach, J.
Phalgun B. Joshi, et al.	Art Unit: 1632
Application No.: 09/295,663	Declaration of Ian MacLachlan Under 37 C.F.R. §1.132
Filed: April 21, 1999	
For: COMBINATION THERAPY USING NUCLEIC ACIDS AND CONVENTIONAL DRUGS	

Considered 5/13/03 JW

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Ian MacLachlan, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true and statements made on information or belief are believed to be true.

2. I hold a Ph.D. (1994) from the University of Alberta, and a Bachelor of Science (1988) from the University of Alberta. I am presently the Chief Scientific Officer for Protiva Biotherapeutics, Inc. (Burnaby, Canada).

3. My field of expertise is gene delivery and gene therapy. I have authored nineteen publications in the field of gene delivery technology, gene therapy, and molecular genetics, and am a member of the American Society of Gene Therapy and

the Science Council of British Columbia, Health Technology Committee. A true copy of my Curriculum Vitae is attached hereto as Exhibit A.

4. The present invention relates to methods for introducing a nucleic acid encoding a foreign gene into cells in a patient, wherein transfection efficiency is increased by at least 50%. The methods involve administering a cell cycle blocking agent to the patient and administering the nucleic acid to the patient after administering the cell cycle blocking agent. The cell cycle blocking agent is a member selected from the group consisting of cyclophosphamide, taxol, taxolene, and a vinca alkaloid. The invention further relates to cancer therapy and, in particular, to methods of introducing nucleic acids encoding foreign genes into a cell in a patient having cancer.

5. I am a named inventor on the above-referenced patent application. I have read and am familiar with the contents of the subject patent application. I have also read the Office Action received from the United States Patent and Trademark Office dated October 22, 2002 and the references cited therein. It is my understanding that the Examiner is concerned that the claimed methods are anticipated or obvious in view of the cited references. Specifically, the Examiner alleges that the claimed invention is anticipated by Son *et al.*, *Proc. Natl. Acad. Sci.* (1994), 91:12669-12672. The Examiner also alleges that the claimed invention is obvious in view of the combinations of Son *et al.*, and Roth *et al.* (U.S. Patent No. 5,747,469), or Son *et al.*, Roth *et al.*, and Walker *et al.* (U.S. Patent 6,041,252), or Roth *et al.*, Son *et al.*, and Bally *et al.* (US Patent 5,705,385).

6. This declaration is provided to demonstrate that the claimed methods are not anticipated by or obvious in view of the cited references. In particular, this declaration is provided to demonstrate that (1) the cited references do not disclose all of the elements of the claimed methods, and (2) that the cited references do not provide any motivation for one of skill in the art to combine their teachings. Furthermore, this declaration is provided to demonstrate that the combination of the cited references would not lead to the claimed invention.

7. Son *et al.*, *Proc. Natl. Acad. Sci.* (1994), 91:12669-12672

Son *et al.* is cited by the Examiner as teaching that cell cycle blocking agents can increase transfection efficiency by at least 50%. In fact, Son *et al.* disclose that only one cell cycle blocking agent, *i.e.*, cisplatin was effective in sensitizing cells to transfection. Son *et al.* explicitly state that "only cisplatin could significantly sensitize the tumor for *in situ* lipofection" (page 12671, right hand column). Son *et al.* also present data showing that only cisplatin sensitizes tumors for *in situ* lipofection (Fig. 4). Moreover, Son *et al.* teach that ***several*** other anticancer drugs such as methotrexate, etoposide, cytosine arabinonucleoside, doxorubicin, and carboplatin (a geometric isomer of cisplatin) had no effect on transfection (page 12671, right hand column and Figure 4). Son *et al.*'s own interpretation of the data presented in Figure 4 explicitly states that:

> Fig. 4 shows that only cisplatin could significantly sensitize the tumor for *in situ* lipofection. Other anticancer drugs including methotrexate, etoposide, cytosine arabinonucleoside, doxorubicin, and vincristine had no effect. Transplatin, a geometric isomer of cisplatin that has no anticancer activity also showed no effect.

Thus, based on Son *et al.*'s explicit statements, the cited reference does not disclose all of the elements of the present invention because, in contrast to the claimed invention, Son *et al.* teach that only cisplatin would be useful for methods of introducing a nucleic acid into cells in patient.

Thus, Son *et al.* fail to disclose all of the elements of the claimed methods of introducing a nucleic acid to cells in a patient using the cell cycle blocking agents recited in the claims (*i.e.*, cyclophosphamide, taxol, taxolene, and a vinca alkaloid), and do not anticipate the claimed invention.

8. Roth *et al.* (U.S. Patent No. 5,747,469)

Roth *et al.* is cited by the Examiner as generally teaching methods and conditions that meet the limitations encompassed by the present claims. However, Roth *et al.* disclose contacting cells with agents such as cisplatin, doxorubicin, etoposide, verapamil, podophyllotoxin, and 5-fluorouracil (*see*, claims 4, 6, 8, 10, 11, and 12,

respectively). Roth *et al.* thus fail to disclose the use of any of the cell cycle blocking agents recited in the claims of the present invention.

9. Walker *et al.* (U.S. Patent 6,041,252)

Walker *et al.* is cited by the Examiner as teaching general methods for improving the delivery of liposomal compositions. Walker *et al.* disclose the use of electrical fields to deliver therapeutic agents encapsulated in a liposome (*see e.g.*, Abstract). Walker *et al.* explicitly state that the encapsulated agents are used to directly kill tumor cells and that "agents are administered in multiple cycles to kill cells as they enter the correct cell cycle phase" (*see,* col. 36, lines 15-19). Walker *et al.* contains no mention or suggestion of the use of any cell blocker or the introduction of a nucleic acid into a cell. Walker *et al.* does not even contain the words "nucleic acid."

10. Bally *et al.* (US Patent 5,705,385)

Bally *et al.* is cited as teaching general methods for improving gene delivery methods. Bally *et al.* do not disclose the use of ***any*** claimed cell cycle blocking agents: cyclophosphamide, taxol, taxolene, vinblastine, vincristine, vinorelbine, and a vinca alkaloid. In fact, there is no mention or suggestion in Bally *et al.* of the use of ***any*** cell cycle blocking agent.

11. Son *et al.*, and Roth *et al.*

Claims 38,-44, 47, 54, 69-73, 79-81, and 83-86 are rejected under 35 U.S.C. § 103(a) as unpatentable over Son *et al.* and Roth *et al.* (U.S. Patent No. 5,747,469)

As discussed in detail above, Son *et al.* do not disclose all of the elements, features or limitations of the presently claimed invention because, in contrast to the present invention, Son *et al.* teach away from the use of drugs other than cisplatin to enhance transfection efficiency. For example, Son *et al.* explicitly state that ***only*** cisplatin significantly sensitizes tumor cells for transfection and that other anticancer drugs, including vincristine, have no effect on transfection efficiency (*see, e.g.*, page 12671, right hand column). Son *et al.*'s interpretation of their own data explicitly states

that: "Fig. 4 shows that only cisplatin could significantly sensitize the tumor for in situ lipofection. Other anticancer drugs including methotrexate, etoposide, cytosine arabinonucleoside, doxorubicin, and vincristine had no effect. Transplatin, a geometric isomer of cisplatin that has no anticancer activity also showed no effect." Thus, if anything, Son *et al.* teach away from the present invention, *i.e.*, Son *et al.* teach away from the use of the compounds recited in the claimed invention (*e.g.*, cyclophosphamide, taxol, taxolene, vinblastine, vincristine, vinorelbine, and a vinca alkaloid). In view of the teachings of Son *et al.*, one of skill in the art would have ***no motivation*** to use any drug except cisplatin to improve transfection efficiency.

Roth *et al.* does not remedy the defect in Son *et al.* In contrast to the claimed invention, Roth *et al.* disclose contacting cells with agents such as cisplatin, doxorubicin, etoposide, verapamil, podophyllotoxin, and 5-fluorouracil (*see,* claims 4, 6, 8, 10, 11, and 12, respectively). Roth *et al.* thus fail to disclose the use of any of the cell cycle blocking agents (*e.g.*, cyclophosphamide, taxol, taxolene, vinblastine, vincristine, vinorelbine, and a vinca alkaloid) recited in the claims of the present invention. Therefore, even if the teachings of Son *et al.* and Roth *et al.* were combined, the combination would not lead to the claimed invention because the references, either alone or in combination, fail to teach or suggest introducing a nucleic acid encoding a foreign gene into a cell in a patient by administering any of the cell cycle blocking agents recited in the present claims.

12. Son *et al.*, Roth *et al.*, and Walker *et al.*

Claims 38-44, 47-54, 69-73, and 78-86 are rejected under 35 U.S.C. § 103(a) as unpatentable over Son *et al.*, Roth *et al.*, and Walker *et al.* (U.S. Patent 6,041,252). In making the rejection, the Examiner alleges that Walker *et al.* disclose the general methods for improving delivery of liposomal compositions and concludes that one of skill in the art would be motivated to combine the nucleic acid and agent in one liposome for a single delivery vehicle.

As discussed in detail above, Son *et al.* teach away from the claimed invention. Therefore, one of skill in the art would have no motivation to combine Son *et al.* and Roth *et al.* Moreover, even if Son *et al.* and Roth *et al.*, were combined, the combination would not lead to the claimed invention because the combination of Son *et*

al. and Roth *et al.* does not disclose any of the cell cycle blocking agents recited in the present claims. Walker *et al.* do not cure the deficiency of Son *et al.* and Roth *et al.* Walker *et al.* disclose the use of electrical fields to deliver therapeutic agents encapsulated in a liposome (*see e.g.*, Abstract). Walker *et al.* explicitly state that the encapsulated agents are used to directly kill tumor cells and that "agents are administered in multiple cycles to kill cells as they enter the correct cell cycle phase" (*see,* col. 36, lines 15-19). Walker *et al.* contains no mention or suggestion of the use of any cell blocker or the introduction of a nucleic acid into a cell. Walker *et al.* does not even contain the words "nucleic acid." Therefore, one of skill in the art would not have had the motivation to combine Walker *et al.* with Son *et al.* and Roth *et al.* Even if one of skill in the art were to combine Son *et al.*, Roth *et al.*, and Walker *et al.*, the combination would not lead to the claimed method of introducing a nucleic acid into cells in a patient.

13. Roth *et al.*, Son *et al.*, and Bally *et al.*

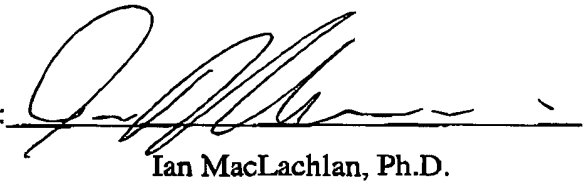
Claims 74-77 and 87 are rejected under 35 U.S.C. § 103(a) as unpatentable over Roth *et al.*, Son *et al.*, and Bally *et al.* (US Patent 5,705,385). In making this rejection, the Examiner alleges that Bally *et al.* teach general methods for improving gene delivery methods and that Son *et al.* provides motivation for one of skill in the art to optimize gene delivery protocols.

As discussed in detail above, Son *et al.* teach away from the claimed invention. Therefore, one of skill in the art would have no motivation to combine Son *et al.* and Roth *et al.* Moreover, even if Son *et al.* and Roth *et al.*, were combined, the combination would not lead to the claimed invention because the combination of Son *et al.* and Roth *et al.* does not disclose any of the cell cycle blocking agents recited in the present claims. Bally *et al.* fail to cure this deficiency. Bally *et al.* do not disclose the use of ***any*** claimed cell cycle blocking agents: cyclophosphamide, taxol, taxolene, vinblastine, vincristine, vinorelbine, and a vinca alkaloid. Moreover, there is no mention or suggestion in Bally *et al.* of the use of a cell cycle blocking agent. Therefore, one of skill in the art would not have had the motivation to combine Bally *et al.* with Son *et al.* and Roth *et al.* Even if one of skill in the art were to combine Son *et al.*, Roth *et al.*, and Bally, *et al.*, the combination would not lead to the claimed method of introducing a

nucleic acid encoding a foreign gene into a cell in a patient, by administering the cell cycle blocking agents recited in the present claims.

14. In view of the foregoing, it is my scientific opinion that none of the cited references alone, or in combination, disclose all of the elements and limitations of the presently claimed invention. It is also my scientific opinion that one of skill in the art would not be motivated to combine the cited references. Therefore, the cited references do not anticipate the claimed invention, nor do they render it obvious.

15. The Declarant has nothing further to say.

Dated: Feb 20, 2003 By: 

Ian MacLachlan, Ph.D.

Curriculum Vitae

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Education

May 1988 - June 1994	Ph.D. (Biochemistry), University of Alberta, Edmonton, Canada, & Department of Molecular Genetics, University of Vienna, Austria.
September 1985 - May 1988	B.Sc. (Biochemistry) University of Alberta, Edmonton, Canada.
September 1982 - May 1984	Biological Sciences University of Calgary, Calgary, Canada.

Experience

Sept 2000 – Present Protiva Biotherapeutics, Inc. 150-8900 Glenlyon Parkway Burnaby, B.C.	Chief Scientific Officer Non-viral Gene Transfer
July 1996 – Aug 2000 Inex Pharmaceuticals Corporation 100-8900 Glenlyon Parkway Burnaby, BC	Team Leader / Research Scientist Non-Viral Cancer Gene Therapy Suicide Gene Therapy, Tumor Biology Vector Development, Inducible Gene Expression
July 1994 - June 1996 Howard Hughes Medical Institute University of Michigan Ann Arbor, MI Supervisor: Dr. G.J. Nabel	Research Fellow, Department of Internal Medicine TNF Mediated Activation of NF-κB Adenoviral Gene Therapy for Restenosis Role of NF-κB in Vertebrate Development
May 1988 - June 1994 Lipid and Lipoprotein Research Group University of Alberta & Dept. of Molecular Genetics University of Vienna Supervisor: Dr. Wolfgang Schneider	Ph.D. Thesis Research: Characterization of receptor mediated uptake of riboflavin binding protein including cloning and characterization of the *rd* mutant.
January - April 1988 University of Alberta Supervisor: Dr. Wayne Anderson	Research: Computerized sequence analysis of lipoproteins, protein crystallography.
September - December 1987 University of Alberta Supervisor: Dr. Wolfgang Schneider	Research: Purification and characterization of apolipoprotein VLDL-II.

EXHIBIT A

Summer 1987 Bamfield Marine Station, Canada Supervisor: Dr. Ron Ydenberg	Research: Behavioral analysis of the polychaete, *Eudystilia vancouveri.*
May 1983 - December 1986 Canadian Hunter Exploration Ltd. Supervisor: Murray Grigg 605 5th Ave. Calgary, Alberta.	Computer programming of oil and gas reservoir simulations and data analysis tools for an oil and gas company.

Additional Training

June – September 1998 Leadership Edge Consulting	Lab-to-Leader Training Program Project Management, Coaching, Team Management
October 1997 Pape Management Consulting	Project Management Training II
February 1997 Pape Management Consulting	Project Management Training I

Awards

1995- 1998	Medical Research Council of Canada Fellowship
1993	Mary Louise Imrie Graduate Award, Faculty of Graduate Studies and Research, Vice-President (Research), University of Alberta
1992 - 1994	Austrian Fonds zur Förderung der Wissenschaftlichen Forschung (Austrian Ministry of Science Scholarship)
1989 - 1993	Heart and Stroke Foundation of Canada Research Trainee
1982	Rutherford Scholarship

Memberships and Affiliations

1998 -Present	American Society of Gene Therapy, Member
1999 -Present	Science Council of British Columbia, Health Technology Committee Member

Patents Applied For

Finn, J., MacLachlan, I., Autogene Nucleic Acids Encoding a Secretable RNA Polymerase, Filed 2001.

MacLachlan, I., Graham, R.G., Systemic Delivery of Serum Stable Plasmid Lipid Particles for Cancer Therapy, Filed 1998.

MacLachlan, I., Buchkowski, S.S., Sensitizing Cells T Compounds Using Lipid Mediated Gene and Compound Deliv ry, Filed 1998.

Joshi, P.J., Mortim r, I.C., Tam, P., MacLachlan, I., Graham, R.G., Combination Therapy of Nucleic Acids and Conventional Drugs, Filed 1998.

Publicati ns

MacLachlan, I., Tam, P., Lee, D., Thompson, J., Giesbrecht, C., Lee, A., Thompson, V., Graham, R.G., A Gene Specific Increase in the Survival of Tumor Bearing Mice Following Systemic Non-viral Gene Therapy, Submitted.

Buchkowsky, S.S., MacLachlan, I., Graham, R.W., Liposomal Encapsulation of Ganciclovir Results in Improved Pharmacokinetics and Biodistribution, Submitted.

Cullis, P.R., MacLachlan, I., Fenske, D.B., Lipid Based Systems for Systemic Gene Therapy, Journal of Liposome Research, In Press.

Fenske, D.B., MacLachlan, I., Cullis, P.R., Stabilized Plasmid-Lipid Particles: a Systemic Gene Therapy Vector, Methods in Enzymology, Academic Press, San Diego, In Press.

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MacLachlan, I., Cullis, P.R., Graham, R.G., Progress Towards a Synthetic Virus for Systemic Gene Therapy, Current Opinion in Molecular Therapeutics, 1: 252-249, 1999.

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Wu, B., Woffendin, C., MacLachlan, I., Nabel, G.J., Distinct Domains of IκB-α Inhibit Human Immunodeficiency Virus Type I Replication Through NF-κB and Rev, J. Virology, 71(4):3161-3167, 1997.

MacLachlan, I., Steyrer, E., Hermetter, A., Nimpf, J., Schneider, W. J., Molecular Characterization of Quail Apolipoprotein II: Disulphide-bond Mediated Dimerization is Not Essential For Inhibition of Lipoprotein Lipase. Biochem. J. 317: 599-604, 1996.

Elkin, R.G., MacLachlan, I., Hermann, M., Schneider, W.J., Characterization of the Japanese Quail Oocyte Receptor for Very Low Density Lipoprotein and Vitellogenin, J. Nutrition, 125: 1258 - 1266, 1995.

MacLachlan, I., Nimpf, J., Schneider, W. J., Japanese Quail Apo-VLDL-II: cDNA Sequence and Comparison to Chicken Apo-VLDL-II, a Specific Inhibitor of Lipoprotein Lipase. Atherosclerosis: 109: 62,1994.

MacLachlan, I., Schneider, W.J., Avian Riboflavin Binding Protein Binds to Lipoprotein Receptors in Association With Vitellogenin. J. Biol. Chem., 269: 24127-24132, 1994.

MacLachlan, I., Nimpf, J., White, H.B. , Schneider, W.J., Riboflavinuria in the *rd* Chicken: 5' -Splice Site Mutation in the Gene for Riboflavin Binding Protein, J. Biol. Chem. 268 : 23222-23226, 1993.

MacLachlan, I., Nimpf, J., Schneider, W.J., A Point Mutation in the Gene for Riboflavin Binding Protein Leads to Activation of Alternate Splicing Pathways Causing Riboflavinuria in the *rd* Chicken. Fed. Amer. Soc. Exper. Biol. Jour., 7: A1091, 1993.

Schneider, W.J., Vieira, A.V., MacLachlan, I., Nimpf, J., Lipoprotein Receptor Mediated Oocyte Growth. In: *Cellular Metabolism of the Arterial Wall and Central Nervous System; Selected Aspects*; Schettler, G., Greten, H. ,Habenicht , A.J.R. (Eds.) Springer-Verlag, Berlin, 1993.

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